REMARKS

This responds to the Office Action mailed on January 24, 2007.

Claim 23 has been canceled without prejudice to its later prosecution and new claim 24 has been added. As a result, claims 1-5, 7, 9-18, 20-22 and 24 are now pending in this application.

Support for new claim 24 can be found throughout the specification and claims. For example, support for claim 24 can be found in claim 23 and in the Examples (see, e.g., page 27).

Claims 9 and 16 are amended. Claim 9 has been amended to specify that the label is covalently attached to the external surface of the microsphere. Support for this subject matter can be found throughout the specification and claims as originally filed, for example, in Figure 1 and the Examples (see, e.g. page 34, last paragraph). The dependency of claim 16 has been amended from 7 to 15, thereby correcting an inadvertent typographical error.

Applicant submits that no new matter has been added to the specification or claims.

Election/Restriction

The Examiner has withdrawn claim 23 from prosecution because claim 23 is drawn to proteinoid microspheres made from a subset of amino acids and the label is allegedly not covalently linked to the microsphere. Applicants have canceled claim 23 and substituted new claim 24 therefor. New claim 24 has the language of claim 23 but explicitly states that the label is covalently linked to the proteinoid microsphere. Applicant submits that claim 1 is generic to new claim 24 because claim 1 is directed proteinoid microspheres made from all amino acids whereas claim 24 is directed to proteinoid microspheres made from a particular subset of amino acids (i.e., a mixture of aspartic acid, glutamic acid, asparagine, arginine, and serine amino acids). Moreover, the labels of claims 1 and 24 are both covalently linked to the proteinoid microspheres. Accordingly, Applicant submits that claim 24 is properly part of the claimed invention and requests confirmation thereof.

§112 Rejection of the Claims

Claim 16 has been rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Examiner has stated that insufficient antecedent basis exists for "the signal amplification." The dependency of claim 16 has been amended to correct an inadvertent typographical error – claim 16 now depends from claim 15 rather than from claim 7. Applicant submits that antecedent basis exists in claim 15 for the term "signal amplification" and that this rejection should be withdrawn.

The Examiner has also stated that it is unclear what signal is intended. Applicant submits that correction of the dependency has clarified this issue. As clearly indicated by the language of claim 16, labeled proteinoid microspheres are useful for signal amplification and provides better signal amplification than an antibody attached to the same label. For example, many labels or dye molecules can be attached to the proteinoid microsphere without adversely influencing its structure, solubility or other properties, whereas one of skill in the art can attach only limited numbers of labels or dyes to antibodies without adversely affecting the antibody structure. Moreover, one of skill in the art must choose antibody-label attachment sites carefully to avoid negatively influencing the functioning (e.g., binding) of the antibodies.

Applicant requests withdrawal of this rejection of claim 16 under 35 U.S.C. § 112, second paragraph.

§103 Rejection of the Claims

Claim 1 is drawn to a labeled proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; wherein the label is covalently linked to an external surface of the proteinoid microsphere; and the proteinoid microsphere is stable in solution.

Applicant traverses the section 103 rejections as described below.

Lohrmann, Steiner and Kayyem

Claims 1, 2, 5, 7, 9, 12-18, 20-22 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Lohrmann et al. (U.S. Patent 6,193,953, "Lohrmann") in view of

Steiner et al. (U.S. Patent 4,925,673, "Steiner") and Kayyem et al. (U.S. Patent 6, 232, 295, "Kayyem"). The Examiner has alleged that this combination of references teaches the invention and has asserted that Applicant must distinguish the invention from the combination of references rather than from each reference individually.

Applicant traverses this rejection on at least four grounds. First, the combination of cited references fails to teach the invention because it fails to teach a proteinoid microsphere with an external, covalently-linked label. Second, teachings on microparticles made from proteins (e.g., Lohrmann) are irrelevant to, and cannot disclose, proteinoid microspheres because the physical and chemical properties of proteinoid microspheres and protein microparticles are different. Hence, one of skill in the art would not apply information gleaned from protein microparticles to make, use or modify proteinoid microspheres. Third, the Steiner reference teaches away from proteins and would therefore discourage one of skill in the art from combining the Steiner teachings on proteinoid microspheres with the Lohrmann and Kayyem teachings on protein microparticles and protein polymeric delivery agents. Fourth, contrary to the Examiner's allegation, one of skill in the art would not have a reasonable expectation of making the protein microparticles of Lohrmann by condensing amino acids as disclosed by Steiner.

Failure to Teach External Labeling: Applicant submits that the combination of references fails to teach a proteinoid microsphere with an external, covalently-linked label. In particular, the Lohrmann and Steiner references are limited encapsulation of contrast agents (e.g. gases or liquids) and pharmacological agents, respectively, where none of the gases, liquids or pharmacological agents is covalently attached to any form of microsphere or microparticle. Kayyem discloses polymers ionically-associated with paramagnetic contrast agents. Applicant submits that such a combined teaching on non-covalently encapsulated air/liquids, non-covalently encapsulated pharmacological agents and polymers ionically-associated with paramagnetic contrast agents is not a disclosure of a labeled proteinoid microsphere, especially when the label is covalently attached to the exterior of the proteinoid microsphere.

Applicant notes that the Examiner has cited to col. 15, lines 1-16 of Lohrmann as allegedly disclosing radiolabeling of the Lohrmann microparticles, for example, with ^{125}I. However, this text explicitly states that such radiolabels are incorporated into the "core" of

microparticles. Therefore, this disclosure by Lohrmann also fails to disclose covalent attachment of a label to the exterior of a microparticle.

The Examiner also states that Kayyem discloses that "a contrasting agent (label) is covalently attached to the polymeric delivery vehicle" (Office Action at 5, Jan. 24, 2007). However, as described by Kayyem contrast agents are paramagnetic ions typically associated or complexed with a chelating agent (see, col. 5, line 11 to col. 6, line 5, FIG. 4). Hence, there is no covalent linkage between the contrast agents and polymers of Kayyem. Thus, the delivery agents of Kayyem are more properly described as "complexes" of polymers and contrast agents, than polymers covalently-attached to labels. Applicant submits that such teachings on polymer-contrast agent complexes disclose nothing relevant to the present invention.

Applicant concludes that the combination of Lohrmann, Steiner and Kayyem therefore fails to disclose a proteinoid microsphere with an external, covalently-linked label.

Disclosure/Teachings on Protein Microparticles Do Not Disclose the Invention. The Examiner has indicated that Lohrmann is the primary reference and that Lohrmann discloses protein microparticles that can be comprised of chemically synthesized amino acid polymers (citing col. 5, lines 40-57). However, such protein/peptide microparticles do not have the same chemical and physical properties as the present proteinoid microspheres. The present proteinoid microspheres are made by thermal condensation of amino acids, which yields a thermally-stable, protease-resistant microsphere. In contrast, the microparticles of Lohrmann are made from proteins or chemically synthesized amino acid polymers (i.e. peptides) and unless such protein microspheres are first "metal stabilized," they will be "irreversibly damaged" during heat treatment.

> Without prior metal stabilization, microspheres are irreversibly damaged by temperatures above 75° C. Lohrmann et al., col. 6, lines 13-16.

In contrast, the present proteinoid microspheres are formed by, and stable at, temperatures of 190 - 220° C for extended periods of time, for example, nine to twelve hours (see, page 28, lines 1-7). Therefore, the proteins and chemically-synthesized amino acid polymers of Lohrmann cannot be thermally condensed to generate any form of stable microsphere. Moreover, the biological

properties of proteinoid microspheres are significantly different from those of protein microparticles as indicated by Steiner:

> [P]roteinoids are far more resistant than proteins to cleavage by digestive enzymes. Steiner, col. 3, lines 27-29.

Hence, use of protein and peptides to make microparticles so dramatically affects the physical and chemical properties of the microparticle, that such microparticles cannot be deemed to be a disclosure of the presently claimed proteinoid microspheres, and any teachings on such protein microparticles are irrelevant to the present invention because those teachings would fail to motivate the skilled artisan to make proteinoid microspheres by thermal condensation of amino acids. Accordingly, Lohrmann not only fails to disclose proteinoid microspheres but when combined with Steiner, this combination fails to motivate one of skill in the art to make the present invention.

Thus, one of skill in the art would conclude from the teachings of Steiner and Lohrmann that protein microspheres are different from proteinoid microspheres, and that the teachings of Lohrmann are inapposite to the teachings of Steiner.

Steiner Teaches Away from Lohrmann and Kayyem: Applicant submits that Steiner teaches away from protein and polymer based delivery agents and thus one of skill in the art would have no motivation to combine the Lohrmann, Steiner and Kayyem references. For example, Steiner discloses the following:

> Among the numerous pharmacological agents which are known to be adversely affected or rendered ineffective when administered orally are the biologically active polypeptides and proteins, such as insulin. These agents are rapidly destroyed in the stomach by acid hydrolysis and in the stomach and lower gastrointestinal tract by enzymes capable of cleaving peptide bonds and, in addition, they pass poorly, if at all, through the gastrointestinal wall. Steiner, col. 1, lines 30-38.

> A great deal of effort has been concentrated on the modification or isolation of the deleterious conditions within the gastrointestinal tract so that a pharmacological agent, which otherwise would be labile, could be absorbed through the stomach or intestine wall intact and in pharmacologically active form. The search in this area has been directed primarily in three directions; the co-administration of adjuvants, such as the resorcinols and the non-ionic surfactants ... the co-administration of

> enzymatic inhibitors, such as pancreatic trypsin inhibitor, diisopropylfluorophosphate (DFP) and trasylol; and the use of liposomes, ... In spite of these demonstrations of limited operability, the use of liposomes is still in the development stage and there are continuing problems, including poor stability and inadequate shelf life. Steiner, col. 1, lines 39-64.

Accordingly, Steiner teaches away from administration of polypeptides and proteins and cautions one of skill in the art that such polypeptides and proteins are labile and subject to hydrolysis. Steiner further states that (unlike polypeptides and proteins) proteinoid microspheres are resistant to cleavage by digestive enzymes.

> [P]roteinoids are far more resistant than proteins to cleavage by digestive enzymes. Steiner, col. 3, lines 27-29.

Steiner therefore teaches away from use of proteins and, accordingly, away from Lohrmann's protein microparticles and the protein-based polymeric delivery agents of Kayyem.

No reasonable Expectation of Success: The Examiner has suggested that because Lohrmann discloses that protein microparticles can be comprised of synthesized amino acid polymers, Lohrmann can be combined with Steiner, which allegedly teaches that proteinoid microspheres are man made condensation polymers (Office Action at 5 (Jan. 24, 2007)). However, Lohrmann specifically discloses "chemically synthesized amino acid polymers" (col. 5, lines 53-57). Such a disclosure that the amino acid polymers are "chemically" synthesized immediately guides one of skill in the art away from any inclination to thermally condense amino acids. Hence, contrary to the Examiner's allegations, one of skill in the art would not have a reasonable expectation of forming the protein microparticles of Lohrmann by condensing amino acids as taught by Steiner. Instead, one of skill in the art would follow the explicit disclosure of Lohrmann and make any such "amino acid polymers" chemically, by well-known peptide synthesis procedures.

Combination of References: The Examiner has alleged that this combination of references teaches the invention and has asserted that Applicant must distinguish the invention from the combination of references rather than from each reference individually. Contrary to the

Examiner's allegations, Applicant is not distinguishing the invention from each individual reference. Instead, Applicant is systematically explaining what the each reference discloses and articulating what differences exist between the combined teachings of the references and the presently claimed invention.

Applicant submits that the Examiner is using the invention as a blueprint to pick and choose words from the language of various references and thereby assemble a facsimile of the present invention. Applicant reminds the Examiner that such hindsight reconstruction of the invention is impermissible.

Accordingly, the present claims are not disclosed, taught or suggested by the combination of Lohrmann et al. (U.S. Patent 6,193,953) in view of Steiner et al. (U.S. Patent 4,925,673) and Kayyem et al. (U.S. Patent 6, 232, 295) and Applicant respectfully requests withdrawal of this rejection of claims 1, 2, 5, 7, 9, 12-18, 20-22 under 35 U.S.C. § 103(a).

Lohrmann, Steiner, Kayyem and Mathiowitz

Claims 3, 4, 10 and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lohrmann in view of Steiner and Kayyem and further in view of Mathiowitz et al. (U.S. Patent 5,271,961). According to the Examiner, Mathiowitz discloses protein microspheres that can be modified by cross-linkers such as glutaraldehyde.

Claim 3 depends from claim 1 and states that the proteinoid microsphere is formed by thermal condensation of the mixture of amino acids in the presence of a crosslinking agent such that the proteinoid microsphere further comprises a crosslinking agent.

The disclosure of crosslinkers by Mathiowitz fails to render the present invention obvious when combined with Lohrmann, Steiner and Kayyem for the following reasons.

First, Mathiowitz is limited to use of a crosslinker for chemical modification of a protein and discloses nothing about thermal condensation of a mixture of amino acids to form proteinoid microspheres while using a crosslinking agent. In contrast to the presently claimed invention, the crosslinkers of Mathiowitz are used to modify the charge of a protein before the protein microspheres are made (see, col. 6, lines 58-62). Thus, one of skill in the are would not be

motivated to form microspheres using crosslinking agents by referring to Mathiowitz, which provides no information whatsoever on the formation of stable microspheres using a crosslinker.

Second, like the Lohrmann and Kayyem disclosures, the Mathiowitz disclosure is limited to protein delivery systems and, as described above, Steiner teaches away from use of such proteins, thereby providing no motivation for combining Steiner with Mathiowitz (as well as with Lohrmann and Kayyem). For example, Steiner teaches that protein microspheres are labile to heat and vulnerable to cleavage (Steiner, col. 1, lines 30-38, col. 3, lines 27-29, col. 6, lines 13-16). Accordingly, one of skill in the art would not seek information about modifying proteinoid microspheres from the teachings of Mathiowitz about labile proteins and protein microspheres.

Third, Mathiowitz teaches away from forming microspheres under harsh conditions and would discourage one of skill in the art from forming microspheres pursuant to the present invention. In particular, Mathiowitz teaches the benefits of using protein microspheres that require only mild conditions for their formation to avoid thermal degradation of the protein and the encapsulated drug (see, e.g., col. 1, lines 23-32). Thus, upon review of Mathiowitz, one of skill in the art would be discouraged from using the thermal condensation methods of Steiner to generate microspheres. Not only does Steiner teach away from use of the proteins recited by Mathiowitz, but Mathiowitz teaches away from using the harsh thermal condensation methods of Steiner. Accordingly, one of skill in the art would combine the teachings of Mathiowitz and Steiner.

Fourth, Mathiowitz fails to disclose external labeling of a microsphere and teaches only the incorporation of compounds into microspheres (see, e.g., col. 2, lines 43-44).

Therefore, the combination of Lohrmann, Steiner, Kayyem and Mathiowitz fails to disclose and/or teach the present invention and Applicant respectfully requests withdrawal of this rejection of claims 3, 4, 10 and 11 under 35 U.S.C. § 103(a)

RESERVATION OF RIGHTS

In the interest of clarity and brevity, Applicant may not have addressed every assertion made in the Office Action. Applicant's silence regarding any such assertion does not constitute any admission or acquiescence. Applicant reserves all rights not exercised in connection with this response, such as the right to challenge or rebut any tacit or explicit characterization of any reference or of any of the present claims, the right to challenge or rebut any asserted factual or legal basis of any of the rejections, the right to swear behind any cited reference such as provided under 37 C.F.R. § 1.131 or otherwise, or the right to assert co-ownership of any cited reference. Applicant does not admit that any of the cited references or any other references of record are relevant to the present claims, or that they constitute prior art. To the extent that any rejection or assertion is based upon the Examiner's personal knowledge, rather than any objective evidence of record as manifested by a cited prior art reference, Applicant timely objects to such reliance on Official Notice, and reserves all rights to request that the Examiner provide a reference or affidavit in support of such assertion, as required by MPEP § 2144.03. Applicant reserves all rights to pursue any cancelled claims in a subsequent patent application claiming the benefit of priority of the present patent application, and to request rejoinder of any withdrawn claim, as required by MPEP § 821.04.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 24 day of April 2007.

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